Busulfan Pharmacokinetics in Adenosine Deaminase-Deficient Severe Combined Immunodeficiency Gene Therapy.

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Public Summary:
Busulfan is a chemotherapy drug used to "make space" in the bone marrow to facilitate engraftment of gene-modified blood-forming stem cells. Results of using busulfan in a series of clinical trials of hematopoietic stem cell gene therapy for adenosine deaminase deficient severe combined immune deficiency (ADA SCID) are reported. Measruing each individual patients levels of busulfan and adjusting subsequent doses leads to more consistent drug levels and engraftment of stem cells.

Scientific Abstract:
The pharmacokinetics of low-dose busulfan (BU) were investigated as a nonmyeloablative conditioning regimen for autologous gene therapy (GT) in pediatric subjects with adenosine deaminase-deficient severe combined immunodeficiency disease (ADA SCID). In 3 successive clinical trials, which included either gamma-retroviral (gamma-RV) or lentiviral (LV) vectors, subjects were conditioned with BU using different dosing nomograms. The first cohort received BU doses based on body surface area (BSA), the second cohort received doses based on actual body weight (ABW), and in the third cohort, therapeutic drug monitoring (TDM) was used to target a specific area under the concentration-time curve (AUC). Neither BSA-based nor ABW-based dosing achieved a consistent cumulative BU AUC; in contrast, TDM-based dosing led to more consistent AUC. BU clearance increased as subject age increased from birth to 18 months. However, weight and age alone were insufficient to accurately predict the dose that would consistently achieve a target AUC. Furthermore, various clinical, laboratory, and genetic factors (eg, genotypes for glutathione-S-transferase isozymes known to participate in BU metabolism) were analyzed, but no single finding predicted subjects with rapid versus slow clearance. Analysis of BU AUC and the postengraftment vector copy number (VCN) in granulocytes, a surrogate marker of the level of engrafted gene-modified hematopoietic stem and progenitor cells (HSPCs), demonstrated gene marking at levels sufficient for therapeutic benefit in the subjects who had achieved the target BU AUC. Although many factors determine the ultimate engraftment following GT, this work demonstrates that the BU AUC correlated with the eventual level of engrafted gene-modified HSPCs within a vector group (gamma-RV versus LV), with significantly higher levels of granulocyte VCN in the recipients of LV-modified grafts compared to recipients of gamma-RV-transduced grafts. Taken together, these findings provide insight into low-dose BU pharmacokinetics in the unique setting of autologous GT for ADA SCID, and these dosing principles may be applied to future GT trials using low-dose BU to open the bone marrow niche.

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